PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 :		(11) International Publication Number:	WO 88/ 0301
A61K 7/00, 47/00	A1	(43) International Publication Date:	5 May 1988 (05.05.88

(21) International Application Number: PCT/EP87/00614

(22) International Filing Date: 19 October 1987 (19.10.87)

(31) Priority Application Numbers: 22105 A/86
48373 A/87

(32) Priority Dates: 23 October 1986 (23.10.86)
10 September 1987 (10.09.87)

(33) Priority Country: IT

(71) Applicant *(for all designated States except US):* ARVAL S.P.A. [IT/IT]; Viale Bligny, 28/30, I-20136 Milano (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* ZAPPIA, Vincenzo [IT/IT]; Via San Giacomo dei Capri, 109/B, I-80131 Napoli (IT). DE ROSA, Mario [IT/IT]; Via E. Nicolardi, 188, I-80131 Napoli (IT).

(74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevet tuale, Via Rossini, 8, I-20122 Milano (IT).

(81) Designated States: AT (European patent), AU, BB, BI (European patent), BG, BJ (OAPI patent), BR, CI (OAPI patent), CG (OAPI patent), CH (European pa tent), CM (OAPI patent), DE (European patent), DK FI, FR (European patent), GA (OAPI patent), GI (European patent), HU, IT (European patent), JP KP, KR, LK, LU (European patent), MC, MG, MI (OAPI patent), MR (OAPI patent), MW, NL (Euro pean patent), NO, RO, SD, SE (European patent) SN (OAPI patent), SU, TD (OAPI patent), TG (OAP patent), US.

Published
With international search report.
Before the expiration of the time limit for amending th claims and to be republished in the event of the receip of amendments.

(54) Title: COSMETIC PREPARATIONS CONTAINING UBIDECARENONES

(57) Abstract

Ubidecarenones are effectively dissolved in aqueous media by means of N-acyl-2-amino-ethanesulphonates, wherein the acyl residues have more than 5 carbon atoms. Cosmetic compositions containing ubidecarenones so solubilized are particularly effective in anti-aging and hydrating treatment.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FR**	France	**ML**	Mali
AU	Australia	**GA**	Gabon	**MR**	Mauritania
BB	Barbados	**GB**	United Kingdom	**MW**	Malawi
BE	Belgium	**HU**	Hungary	**NL**	Netherlands
BG	Bulgaria	**IT**	Italy	**NO**	Norway
BJ	Benin	**JP**	Japan	**RO**	Romania
BR	Brazil	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SN**	Senegal
CH	Switzerland	**LI**	Liechtenstein	**SU**	Soviet Union
CM	Cameroon	**LK**	Sri Lanka	**TD**	Chad
DE	Germany, Federal Republic of	**LU**	Luxembourg	**TG**	Togo
DK	Denmark	**MC**	Monaco	**US**	United States of America
FI	Finland	**MG**	Madagascar		

"COSMETIC PREPARATIONS CONTAINING UBIDECARENONES"

The present invention relates to cosmetic preparations containing soluble ubidecarenones prepared by disperding in acqueous media mixtures having different ratios of ubidecarenones and acyl derivatives of 2-aminoethansulphonic acid.

The ubidecarenones form an important class of liposoluble vitaminic principles, particularly 2,3-dimethoxy-5-methyl-8-decaprenyl-1,4-benzoquinone, known as ubidecarenone-10, localized at the mitochondrial level, plays a key-role in mammals in the electron-transfer system and more generally in the energy production.

Because of said important metabolic roles, the ubiquinone-10 is widely used in a large number of cardiac pathologies, protecting the myocardium from ischemic phenomena and preserving the functions thereof.

Moreover, because of the ability of ubidecarenone-10 of influencing both the tissutal respiration and the peroxidative phenomena of the cellular membranes, said vitamin is particularly interesting for the prevention of tissutal aging phenomena, particularly of the skin, which the recent biochemical knowledges ascribe, inter alia, to the action of free radicals, responsible of the structural alteration of the membrane lipids.

The development of biocompatible, hydrosoluble formulations is of particular interest for a better bioavailability of ubidecarenone-10 both in the pharmaceutical and cosmetic use.

The present invention concerns the development of a

system able to carry in aqueous media the ubidecarenones, thanks to the interaction with amphipatic ions of general formula $RNH-CH_2-CH_2-SO_3$, wherein R is an acyl radical having more than 5 carbon atoms, preferably a natural fatty acid of the normal, iso, anteiso series or cycloalkyl, saturated or unsaturated having from 8 to 26 carbon atoms. This class of amphipatic molecules is surprisingly able to carry the ubidecarenones in water, in form of micellar and/or liposomial aggregates, even using an equimolar ratio of the two compounds.

A molar excess of the amphipatic solubilizing species is preferably used, from 2 to 4 times higher than the vitamin, said conditions granting a better and faster solubilization.

The preparation of hydrosoluble ubidecarenones may be carried out in different ways, for instance by sonicating an acqueous solution of the amphipatic species, to which the ubidecarenone is added or preferably by dispersing in water, under vigorous stirring, a mixture of ubidecarenone and N-acyl-2-amino-ethanesulphonate, prepared by evaporation of a solution of the two compounds in an organic solvent, in which both are soluble.

The micellar and/or liposomial systems so prepared are stable over long periods of time, even at extremely low or high environmental temperatures, that may be moreover lyophilized, yielding generally materials of waxy consistency, easily soluble in water by simple stirring.

The advantages attained by the invention in the cosmetic use are:

a) the possibility of using hydrating, non-oily prepara-

tions, also in combination with other active principles;

b) a good absorption of the active principle by the derma, because of its micellar and/or liposomial organization;

c) a good tolerability even in prolonged treatments;

d) the possibility of sterilizing by filtration the preparation thanks to its reduced size and to the stability of the micellar and/or liposomial aggregates;

e) the possibility of modulating the characteristics of the preparation by changing the acyl residues of the solubilizing agent.

The invention provides therefore cosmetic compositions containing as the active principle compounds of ubidecarenone and N-acyl-2-amino-ethanesulphonates optionally in admixture with conventional cosmetic excipients.

The compositions of ubidecarenone and N-acyl-2-aminoethansulphonates find specific use in the cosmetic field in the prevention of tissutal aging phenomena. Said action exerted by ubidecarenone is to be ascribed to a specific protective mechanism from the peroxidative phenomena on the double bonds of the membrane unsaturated fatty acids and to the specific roles of this vitamin in the cellular respiration processes.

The procedures generally described in the present invention, because of their simplicity or limited cost, are easily suited to the development of preparative processes on the industrial scale.

The cosmetic preparations of the invention are prepared according to well-known methods and using conventional excipients such as those described in "Remington's

Pharmaceutical Sciences", Hack Pub. Co., N.Y., USA. Examples of said preparation are creams, lotions, also in form of sprays, containing from 0.5 to 10% by weight of an hydrosoluble ubiquinone derivative, particularly of ubidecarenone-10.

Other cosmetically active substances may be used in combination with the ubidecarenone derivatives of the invention.

The compositions are applied to the skin in the usual amounts in order to achieve the desired cosmetic effects, for instance anti-aging and hydrating effects, cellular regeneration, stimulation of the hair growth, protection from damages induced by UV radiations, anti-wrinkles and anti-scurf effects.

The following examples illustrate the preparation of different kinds of soluble ubidecarenones. They necessarily concern only some of the numerous possibilities which can be envisaged and, without any limitative character, they only define the scope of the invention.

EXAMPLE 1

62.5 g of 2-amino-ethansulphonate, suspended in 500 ml of anhydrous dimethylformamide, were reacted at 70°C for 10 hours with 410 g of oleic anhydride, in the presence of 0.5 g of dimethylaminopyridine as a catalyst.

After evaporation of the solvent under vacuo, the oily residue was repeatedly triturated in ethyl ether. 190 g of N-oleyl-2-amino-ethansulphonate as a waxy, white solid, were obtained.

The ^{2}H-NMR spectrum in $CDCl_3$ shows the signal of the acyl moiety, in the correct integration ratio, at δ

5.3; 2.4; 1.9; I.r.: 1.3 and 0.9 and those of 2-amino-ethanesulphonate at δ 3.7 and 4.6.

86.2 g of ubidecarenone-10 were added to 81 g of N-oleyl-2-aminoethansulphonate, dissolved in 2.8 liters of water.

The obtained biphasic system, after sonication, yields an homogeneous phase of micellar and/or liposomial kind, stable in time and to the environmental parameters. For instance, freezing of the solution or its heating do not change the chemico-physical state of the dispersed supermolecular aggregates.

EXAMPLE 2

87.5 g of 2-amino-ethanesulphonate, suspended in 500 ml of anhydrous pyridine, were reacted at 50°C for 10 hours with 311 g of linolenic acid chloride.

After evaporation of the solvent under vacuo, the oily residue was first triturated in ethyl ether and then, dissolved in water, was dialyzed against water. After lyophilization 255 g of N-linoleyl-2-amino-ethanesulphonate as a white, waxy solid, were obtained. The H^1-NMR spectrum recorded in $CDCl_3$ shows, in the correct integration ratios the signals of the acyl moiety at δ 5.3; 2.8; 2.4; 1.9;1.6;1.3;0.9 and those of 2-amino-ethanesulphonate at 3.7 and 4.6.

172 g of ubidecarenone-10 and 321 g of N-linoleyl-2-amino-ethanesulphonate were dissolved in 2 l of 1 $CHCl_3$.

After evaporation of the solvent under vacuum, 3.4 liters of water were added under vigorous stirring. An homogeneous system, yellow-orange in colour, of micellar and/or liposomial kind, stable in time and to the environ-

mental parameters was obtained.

EXAMPLE 3

43.1 g of ubidecarenone-10 and 64.2 g of arachidonyl-2-amino-ethanesulphonate were dissolved in 1 l of $CHCl_3$.

After removal of the solvent, 2 l of water were added under vigorous stirring, till the formation of a stable micellar and/or liposomial system. After freezing and lyophilization of the solution a waxy compound orange in colour, readily soluble in the presence of water, was obtained.

CLAIMS

1. Hydrosoluble ubidecarenones derivatives obtained by addition to the ubidecarenones of N-acyl-2-amino-ethane-sulphonate wherein the acyl residue has more than 5 carbon atoms and is preferably a natural fatty acid, saturated or unsaturated of the normal, iso, anteiso or cycloalkyl series, having from 8 to 26 carbon atoms.

2. Cosmetic compositions containing as the active principle an hydrosoluble ubidecarenone derivative according to claim 1, optionally in combination with other active principles, in admixture with the usual excipients and vehicles.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 87/00614

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 7/00; A 61 K 47/00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	FR, A, 2472384 (GOEMINNE B.G.) 3 July 1981 see claims	1,2
P,Y	EP, A, 0211647 (ALLERGAN PHARM. INC.) 25 February 1987 see page 8, lines 3-16; claims	1,2
Y	FR, A, 2322133 (BAYER AG) 25 March 1977 see page 1, paragraph 1; claims	1,2
Y	EP, A, 0069399 (EISAI) 12 January 1983 see claims 1,2,7	1,2

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
8th February 1988	17 MAR 1988
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: P.C.G. VAN DER PUTTEN

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 8700614

SA 19322

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 04/03/88
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 2472384	03-07-81	None	
EP-A- 0211647	25-02-87	JP-A- 62042733	24-02-87
		AU-A- 5914186	24-12-87
FR-A- 2322133	25-03-77	DE-A,B,C 2537914	10-03-77
		US-A- 4071543	31-01-78
		GB-A- 1502519	01-03-78
		CH-A- 605716	13-10-78
		JP-A- 52027719	02-03-77
EP-A- 0069399	12-01-83	JP-A- 58008010	18-01-83
		CA-A- 1197463	03-12-85